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Mathematical Modeling of Spontaneous Calcium Oscillations in Astrocytes

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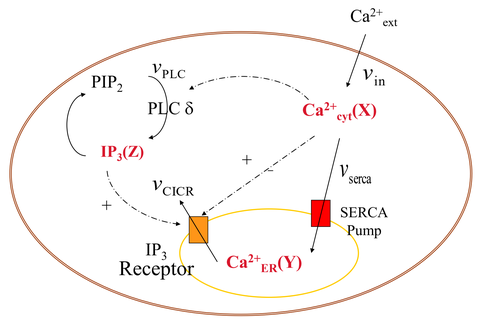
Introduction

Astrocytes are cells that are located in the central nervous system, usually next to neurons. Initially thought of as being a passive structural element that held the neurons together, they are now postulated to play a much more active part in the signaling process. In the cases where neurons and astrocytes are allowed to interact, the changes in the astrocyte's oscillatory Ca^{2+} behavior is found to be a result of external stimulation, such as neurotransmitter reception. Recently, however, it has been observed that Ca^{2+} oscillations in astrocytes can be generated spontaneously, without neuronal intervention. These spontaneous oscillations indicate that astrocytes might regulate neuronal activity [1, 2]. This is especially important in pathological cases. For instance, spontaneous Ca^{2+} oscillations are found in cases of epilepsy [3]. Since this type of regulation has not been studied as extensively as neuronal activity, studying astrocytes might help elucidate many aspects of brain activity.

Abstract

This study presents the key mechanistic steps by which spontaneous Ca^{2+} oscillations can occur in astrocytes. We propose a model for an independent mechanism that incorporates the cytosolic and endoplasmic calcium concentrations. These concentrations are moderated by the flux of calcium ions through the astrocyte's membrane, which also triggers the oscillations. The oscillations are sustained by the interaction of inositol trisphosphate (IP_3) and extracellular, cytosolic, and endoplasmic Ca^{2+}, via the inositol cross-coupling (ICC) and the calcium induced-calcium release (CICR) mechanisms. Our simulations have produced results that are qualitatively similar to experiment. This model shows appropriate frequency, amplitude and behavioral dependencies as parameters controlling the endoplasmic (SERCA) pump rate, IP_3 receptor sensitivity, and protein kinase C (PKC) inhibition are changed.

The Model



Model Equations:

$$\frac{dX}{dt} = v_{in} - k_{out}X + v_{CICR} - v_{serca} + k_f(Y - X) \quad (1)$$

$$\frac{dY}{dt} = v_{serca} - v_{CICR} - k_f(Y - X) \quad (2)$$

$$\frac{dZ}{dt} = v_{PLC} - k_{deg}Z \quad (3)$$

Expansion of Terms:

$$v_{CICR} = 4v_{m3}\left(\frac{k_{ca}^n X^n}{(X^n + k_{ca}^n)(X^n + k_{ca}^n)}\right)\left(\frac{Z^m}{Z^m + k_{ins}^m}\right)(Y - X) \quad (4)$$

$$v_{serca} = v_{m2}\left(\frac{X^2}{X^2 + k_2^2}\right) \quad (5)$$

$$v_{PLC} = v_d\left(\frac{X^2}{X^2 + k_p^2}\right) \quad (6)$$

Parameter Values :

$k_{out} = 0.5/sec$	$n = 2.02$	$v_{m2} = 15.0\mu M/sec$	$k_2 = 0.5/sec$	$k_{deg} = 0.08/sec$
$k_{m3} = 40/sec$	$m = 2.2$	$k_{ins} = 0.1\mu M$	$k_f = 0.5/sec$	$k_p = 0.3\mu M$
$k_{ca} = 0.15\mu M$	$[InsP_3]_{cyt} = 0.1\mu M$	$v_{m2} = 15.0\mu M/sec$	$v_{m3} = 40.0/sec$	$v_{in} = 0.05\mu M/sec$
$[Ca^{2+}]_{cyt} = 0.1\mu M$	$[Ca^{2+}]_{ER} = 1.5\mu M$			

Methods

Simulations were performed using the Rosenbrock and DSLODE routine for the numerical solution of differential equations. The software used was Berkeley Madonna (University of Berkeley, Berkeley, Ca) and DLSODE. [4] All diagrams were produced from the results of the DSLODE routine. The plotting program used is Kaleidagraph (Synergy Software).

Complex Behavior

Although most experimental work shows oscillatory transients similar to period-1 behavior, some studies show more complex oscillations [3,5]. This model, with small changes in parameter values, can go through complex oscillations such as a period adding regime to chaos. The simulations presented here result from variations in parameters which correspond to lowering the affinity for Ca^{2+} in IP_3R dynamics, and initiating a faster response to Ca^{2+} in the PLCδ1 mechanism [2, 6].

Dependence on Parameters

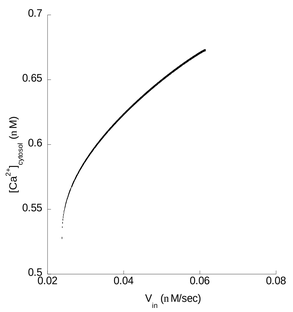


Figure 1. *The single curve on the bifurcation diagram indicates that this model displays period-1 behavior in $[Ca^{2+}]_{cyt}$ throughout the oscillatory window of v_{in} (extracellular flux).*

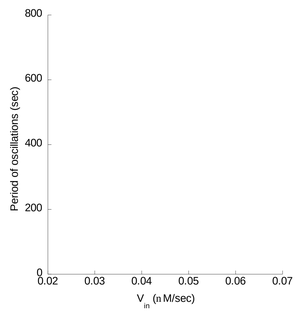


Figure 2. *As the $[Ca^{2+}]_{cyt}$ is increased via v_{in}, the oscillatory period decreases in accordance with experiment [1].*

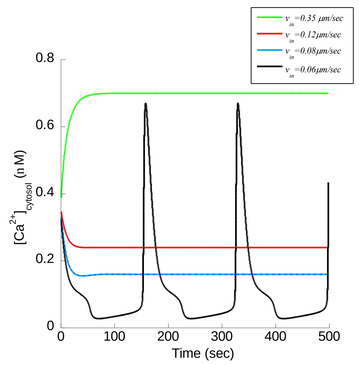
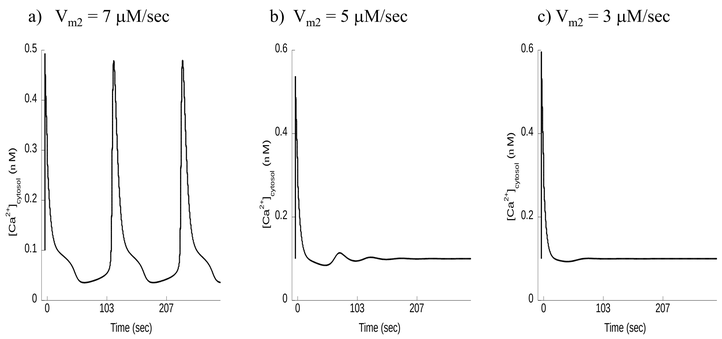


Figure 3. *With an increase in v_{in}, the behavior changes from oscillatory to steady state. The level of the steady state then increases as the flux is augmented.*



Figures 4. *The increasing inhibition of the SERCA pump is modeled by decreasing v_{M2}, the maximum flow rate through the SERCA pump. As v_{M2} is lowered (a-c), the ability to form sustained high amplitude oscillations is diminished. These simulations are in agreement with the experimental results of Nett, Olof, and McCarthy [2].*

Simulations and Analysis

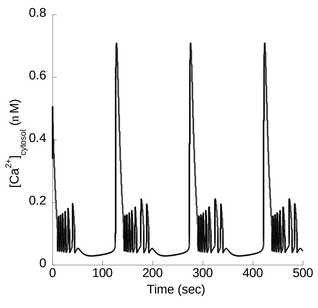


Figure 5. *Time series showing bursting behavior. This type of regime has been found under epileptoform conditions*
Parameters: $K_p = .164$, $K_{ca} = .27$, $V_{in} = 0.05$

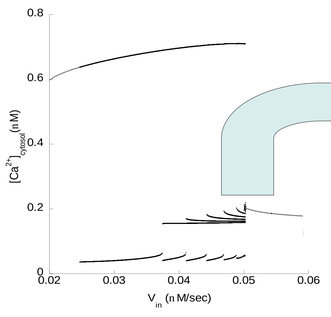


Figure 6. *Bifurcation diagram generated around the same parameter values as Fig. 5. Here, as one increases the extracellular flux (v_{in}), the diagram shows a period adding mechanism.*

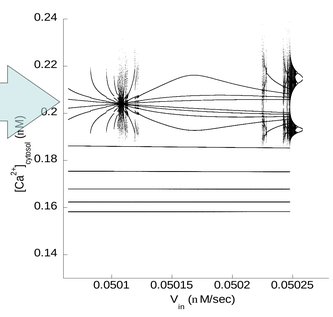


Figure 7. *A more detailed bifurcation diagram over a smaller parameter range. The dark areas suggest chaotic behavior.*

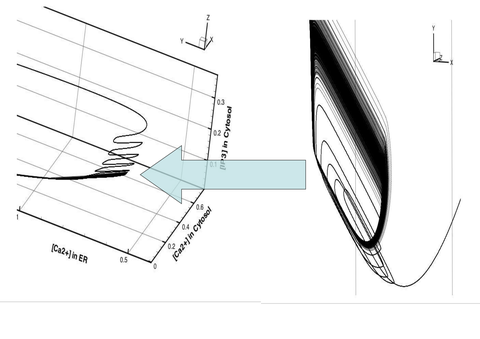


Figure 8. *Phase plane diagrams for v_{in} = .0501067 μM/sec. These diagrams are representative of the first dark region from the left in Fig. 7. The top two diagrams show the axes for the respective calcium concentrations. The units of all three axes are (μM/sec)*

Discussion

The parameter dependence analysis shows that the entry of extracellular Ca^{2+} across the membrane can generate spontaneous oscillations. Furthermore, this flux of calcium resulted in frequency and amplitude dependencies similar to those found in experiments. This model also shows that the key dynamics in the generation and termination of the $[Ca^{2+}]$ spikes involve the activation of PLCδ1 and the initiation of the CICR and ICC coupled mechanisms by the production of IP_3 by PLCδ1. The robust behavior of the model, such as the chaotic regimes, shows that this model is a viable representation of actual biological processes. Thus, the study suggests that the basic mechanisms the mathematical model incorporates are sufficient to generate and regulate spontaneous calcium oscillations. This model can be used to predict how an astrocyte responds to different physiological changes. For instance, it can show what mechanisms in astrocytes are modified under pathological conditions, such as epilepsy. An interesting follow-up experimental study would be a comparison of parameter variation in the model versus actual changes in experimental conditions.

References

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